Clinical decision making in occupational HIV exposure: The role of baseline laboratory testing in the exposed healthcare provider

By

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Contents

Abstract

Objectives

We investigated whether baseline laboratory findings change provider prescribing behavior for HIV post-exposure prophylaxis.

Methods

A retrospective review of occupational health records from a large, tertiary care academic medical center was conducted. Subjects were healthcare providers (HCP) with clinical or research exposure to HIV who completed a 28-day course of once daily tenofovir disoproxil/emtricitabine (245/200 mg) plus twice daily raltegravir (400 mg). Basic demographic information, exposure information and laboratory values were obtained from the medical record.

Results

Between January 1, 2012, and May 12, 2016, 64 HCP completed a 28-day course of post-exposure prophylaxis (PEP). Two HCP presented with laboratory abnormalities at baseline {renal (1), hepatic (1)} and three HCP had abnormal changes at two weeks compared to baseline {renal (2), hematologic (1)}; however, none of the abnormalities led to modification or discontinuation of PEP. There were no HIV seroconversions throughout the study period.

Conclusion

Our five-year experience of prescribing PEP at a large academic medical center suggests that baseline assessment of renal, hematologic and hepatic function is unnecessary when starting the HIV post-exposure prophylaxis regimen of tenofovir disoproxil/emtricitabine/raltegravir. Given that HCP are generally a healthy population, that hepatic or renal dose adjustments are not required for this PEP regimen and that this course of PEP is well-tolerated it appears that baseline laboratory testing is unnecessary. Elimination of routine renal, hematologic and hepatic

function studies in occupational HIV exposures should be considered as a way to improve the timeliness of starting PEP after exposure as well as eliminate the barrier of seeking immediate care after exposure beyond obtaining PEP medications.

Introduction

The prevention of occupationally acquired human immunodeficiency virus (HIV) infection in the US is by all accounts a public and occupational health success story. From 1985 to 2013, there were 58 confirmed cases of occupationally acquired HIV infections in healthcare providers (HCP), with an additional 150 possible cases (CDC Division of HIV/AIDS Prevention). However, with more effective post-exposure prophylaxis (PEP) regimens and improved compliance as therapies have become more tolerable, there has only been one confirmed occupationally acquired HIV infection in a health care worker since 1999 (CDC Division of HIV/AIDS Prevention).

The success in prevention of occupationally acquired HIV infections does not mean that continued efforts are not needed. Approximately 385,000 sharps-related injuries occur each year to hospital-based HCP (CDC, 2011). While sharps-related injuries in nonsurgical hospital settings decreased by 31.6% in the first five years after the Needlestick and Safety Prevention Act of 2000, sharps-related injuries in surgical hospital settings increased by 6.5% over the same time frame (CDC, 2011). The prevalence of HIV is another factor to consider. By the end of 2012, an estimated 1.2 million people aged 13 and older were living with HIV in the United States, including 156,300 (12.8%) people who had yet to be diagnosed (CDC, 2015). This number has been stable from 2010 to 2014, so incidental occupational transmission is still a problem.

HIV continues to be a disease with substantial morbidity and thus it is important to prevent transmission of HIV whenever possible. To this end, HIV PEP has been used since the late 1980s as a way to reduce the chances of HIV seroconversion in exposed individuals. Formal support for HIV PEP medications first appeared in 1996 in the US Public Health Service (PHS)

guidelines (CDC, 1996). Because the HIV medications used in 1996, namely zidovudine (ZDV), lamuvidine (3TC), and indinavir (IDV) exhibited significant toxicity (Lee & Henderson, 2001), early guidelines recommended monitoring of laboratory values for complete blood count, renal, and hepatic function tests at baseline, and at 2 weeks (CDC, 1996). To this day, the New York State Department of Health AIDS Institute, recommends laboratory monitoring at baseline, 2 weeks, and 4 weeks (New York State Department of Health AIDS Institute, 2016).

The medications of the past were not well tolerated due to both high pill burden and toxicity, and this adversely affected adherence (Parkin, et al., 2000). Research has led to many advancements in HIV medications since the support of the initial PEP regimen in 1996. The current standard of care for HIV PEP is a 3-drug regimen of once daily tenofovir disoproxil/emtricitabine (245/200 mg) plus twice daily raltegravir (400 mg) and is neither renally nor hepatically dosed (Kuhar, et al., 2013). This 3-drug regimen is also the preferred combination for antiretroviral-naïve HIV infected pregnant women (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2016) and is recommended for non-occupational post-exposure prophylaxis (nPEP) (McAllister, et al., 2013). While the US Public Health Service guidelines for PEP have been updated 3 times since 1996, the provision for the drug toxicity monitoring has remained unchanged since 1996, despite the greatly improved side effect profile of the current 3-medication PEP regimen (Kuhar, et al., 2013).

The drug toxicity monitoring itself costs money. Given these costs, and the fact that the drug toxicity monitoring provision has not been updated despite the PEP medication advancements, we were interested in exploring whether baseline laboratory findings influenced the course of care for HIV PEP.

Systematic Review of Previous Literature

Introduction

The intent of this systematic review was to identify existing studies that examined baseline laboratory tests (hepatic, renal, and hematologic) in the setting of HIV PEP, and to see how these test results were related to adherence and toxicity. A brief background on the medications that comprise the PEP regimen will be presented followed by the systematic review.

Emtricitabine-tenofovir (FTC-TDF) is a co-formulation that is produced by Gilead Sciences. Emtricitabine is a nucleoside reverse transcriptase inhibitor. Tenofovir is a nucleotide reverse transcriptase inhibitor. Reverse transcriptase is a key viral enzyme made by retroviruses such as HIV and hepatitis B used to convert its RNA into DNA that can then be inserted into the host's DNA.

The combination of emtricitabine-tenofovir gained its first FDA approval in 2004 (FDA.gov, 2016). It is often paired with either a protease inhibitor such as lopinavir (combined with ritonavir), or with an integrase strand inhibitor such as raltegravir. It is FDA approved as a component of HIV therapy. It is also FDA approved for pre-exposure prophylaxis (PrEP) for prevention of HIV infection. Its off-label uses include: hepatitis B treatment in patients with antiviral-resistant HBV or coinfection with HIV, PrEP for prevention of HIV infection in injecting drug users (IDU) who are at risk for parenteral acquisition of HIV but not at risk for sexual acquisition of HIV, and occupational PEP.

Raltegravir (RAL) is a drug in the integrase inhibitor class, and is produced by Merck. It operates by inhibiting virus' integrase enzyme. The enzyme functions to incorporate viral DNA into the genome of the host cell. Raltegravir thus works by inhibiting the integration of viral DNA into the host's DNA. It has a theoretical advantage over protease inhibitors because it halts

the HIV infection process *before* HIV integrates into the host's DNA, as opposed to protease inhibitors which intervene *after* the DNA already has been integrated into the host DNA. Raltegravir was the first approved integrase inhibitor for clinical use in both treatment-naïve and treatment-experienced patients. It gained FDA approval in October 2007 (FDA.gov, 2016). It is FDA approved for treatment of HIV-1 infection in combination with other antiretroviral agents. Off-label usage includes PEP for occupational (and non-occupational) exposure to HIV.

The combination 3 drug regimen of emtricitabine-tenofovir plus raltegravir was first supported in the US Public Health Service Guidelines for PEP in 2013 (Kuhar, et al., 2013). It is now the preferred regimen.

Methods

Search Strategy: PubMED and SCOPUS were searched on June 18, 2016 to identify possible studies. As each database is indexed differently and has a different set of studies, slightly different searches were conducted in each of the databases.

PubMED was searched using the term "raltegravir tenofovir emtricitabine". This produced 138 results. SCOPUS was searched using the term "raltegravir tenofovir emtricitabine (adverse effects OR tolerability OR side effects)". This produced 117 results.

Selection Criteria: Articles chosen for review met the following criteria: involved the HIV raltegravir-tenofovir-emtricitabine regimen, involved human subjects, had been conducted in the last 5 years, be written in English, and contained metrics (either qualitative or quantitative) regarding adherence or tolerability. The full article had to be available via PubMED or SCOPUS. Only data that had been published or presented in a peer-reviewed setting were considered. No case studies or pilot studies were reviewed.

Data Abstraction: Once an article was selected for full review, relevant data points were abstracted by a single author (Chima Ohadugha) from the publication and arranged in a table. These qualifications of the evidence presented are based on the type of study and by limitations to: study quality, consistency, certainty about directness, precision, bias, effect magnitude, statistical significance, and the potential for confounding.

Results

The PubMED search produced 138 results. SCOPUS produced 117 results. These results were placed in RefWorks, and the duplicate studies were removed, as there was some overlap in the studies that were retrieved from the search of the 2 databases. After removing the duplicates, 212 unique references remained. The abstracts of these articles were analyzed to determine the suitability of each article. The references of the articles were examined for relevant articles as well. Most articles were dealt with the incorrect PEP regimen, or did not address issues of adherence or side effects. Three relevant articles remained whose details are provided in Table 1.

Analysis

The first article, the STARTMRK trial, was a randomized, blinded, double-dummy phase III trial (Rockstroh, et al., 2013). It compared raltegravir plus tenofovir/emtricitabine with efavirenz plus tenofovir/emtricitabine over the span of 5 years. The primary outcome was the percentage of subjects with viral RNA levels less than 50 copies/mL. Adherence and side effects were also measured via patient diaries, clinician pill counts, and clinical evaluations. In the study, 281 people were randomized to the raltegravir group. Patients were 81% male, 41% white, with a median age of 37.6 years. The majority of subjects were from the Latin American site (35.2%), with the remaining from Southeast Asia (12.1%), North America (29.2%), and Europe (23.5%).

Drug-related clinical adverse events were reported in 146 raltegravir recipients (52.0%). Laboratory adverse events were reported in 56 patients (19.9%). Zero patients discontinued due to laboratory abnormalities.

A main strength of the study was its design (randomized, blinded). Another strength was that the study reported the number of people who discontinued the treatment due to laboratory abnormalities. A weakness of the study stemmed from the fact that pill counting was used to monitor adherence, as the patients may have done pill-dumping in order to appease the clinician. A potential limitation was that many investigators (Rockstroh, Dejesus, etc.) were paid consultants at various pharmaceutical companies, including Merck and Gilead.

The second article described the QDMRK trial was a randomized, double-blind, phase 3 non-inferiority study (Eron, et al., 2011). Patients were randomly assigned to receive tenofovir-emtricitabine plus either 400mg BID raltegravir or once daily 800mg raltegravir. The primary outcome was virological response at 48 weeks in patients who received at least 1 dose of study drug. Adherence and drug side effects was also monitored.

The patients were from 83 centers on six contents. Most (72%) were white. Eighty-two percent were male. The median age was 38. There were 775 enrolled patients, with 388 randomly allocated to receive raltegravir BID, with the remainder receiving raltegravir once daily. Median time spent in study for the participants was 68 weeks.

Of the BID raltegravir group, 11% had abnormal laboratory values, and 2.3% had *drug-related* laboratory adverse events. In the trial, there were 0 reports of serious drug related adverse effects, and discontinuations due to adverse effects. The most common grade 3 or 4 laboratory abnormalities were increased creatine kinase (5% of participants) without any reported

rhabdomyolysis. Alanine aminotransferase levels were >5 times ULN in 13/386 (3.4%) of participants. Absolute neutrophil count was <750/µL in 5/386 (1.3%) of cases.

A main strength of the study was the study design. Another strength was that the study was designed to report adverse events and laboratory abnormalities explicitly (using MedDRA version 11.0). Potential limitations include the fact that many of the investigators have been paid pharmaceutical consultants. Also Merck has sponsored the study. This may play a role because the investigators were the people who decided whether an adverse effect was drug-related.

The third study, by McAllister et al, dealt with HIV-uninfected men evaluated in Australia for non-occupational PEP (McAllister, et al., 2013). 86 were prescribed the tenofovir-emtricitabine-raltegravir regimen, and 34 were prescribed tenofovir-emtricitabine. Adherence (measured by pill count) and adverse events were assessed at weeks 1, 2 and 4. The study participants received extended education about the importance of adherence. There were non-study controls who chose not to enter the study, who did not receive the extra counselling. The study was a non-randomized, controlled, prospective study.

Adherence rate was 92%. The 91 RAL-FTC-TDF recipients reported 260 adverse events (mean 2.9/person). All subjective adverse events were either grade 1 or 2, and 82% were possibly, probably or definitely related to study drug. Nine percent developed mild myalgias, with 4 developing transient grade 4 elevations in creatine kinase, which spontaneously resolved by week 4. Grade 1−2 elevations in alanine and aspartate aminotransferases occurred in 28 (22%) study participants but grade 3 or 4 was uncommon (2%).

A strength of the study, with regards to our question, is that it examined the HIV medications specifically in the context of PEP. The other 2 studies, in contrast, examined the

HIV medications in the context of persons diagnosed with HIV requiring a lifelong treatment course . A limitation of the study was that the participants received more education about adherence, and text message reminders than perhaps the general population would. Like the other studies, pill count was used for adherence, which is a potential limitation.

Implications of Findings: This review, which includes 755 patients, suggests that the 3-drug regimen is well-tolerated, and that adherence is high. As such, it also suggests that routine laboratory studies for medication-related abnormalities may be unnecessary for short-term PEP. The paucity of studies specifically examining occupational PEP regimens suggests that more attention could be directed towards occupational PEP.

Methods

Data Abstraction

A retrospective chart review of University and Hospital HCP of the University of North Carolina at Chapel Hill evaluated for PEP, between January 1, 2012, and May 12, 2016, was conducted. The University HCP (researchers, students, and anyone with a University faculty appointment) were evaluated at the University Employee Occupational Health Clinic and the Hospital HCP were evaluated at the UNC Hospitals Occupational Health Services. Of note, attendings with faculty appointments are regarded as University HCP. While both occupational health clinics use the same HIV PEP protocol, each clinical site operates independently. Since the data were recorded and organized differently between the two sites, the process of the data abstraction differed, and thus will be discussed for each site individually.

For the University Employee Occupational Health Clinic (Medical Drive) location, a list of HCP who received HIV PEP was not readily available. A list of these HCP was derived as follows. First, a list of HCP who had a filed a workman's compensation report during the years

of interested was gathered. Within this group, HCP who had undergone laboratory tests for blood-borne pathogen exposures (BBPE) were then identified. Of note, this group included HCP who had exposures to a wide array of sources, including unknown sources, known HIV positive sources, known HIV negative sources, and known hepatitis B sources.

All of the medical records of the HCP with BBPE laboratory tests were examined. Most of these were medical charts located within the building (organized in alphabetical order), and some were archived in PDF format on the secured computers within the building. UNC's Personal Identification Number (PID) and name were used to identify each patient. If the chart contained a PEP prescription, then the chart was abstracted and the data was placed in a secured cabinet for subsequent analysis.

For the UNC Hospitals Occupational Health Services (Manning Drive) location, the information for Hospital HCP who were prescribed HIV PEP was stored differently. The HCP medical records (in the form of physical charts or archived compact discs) were located onsite. The charts were all organized by medical record number (MRN).

A list of HCP who received PEP is kept onsite in a set of booklets, separate from the medical records. The booklet contains the employee name, and either the MRN or an internal number called the "Z number". Since the booklets did not always contain the HCP MRNs, we used a separate list called the "Z-list", to map the HCP names to their respective MRNs. The MRN number was then used to locate the charts. If the charts were not found, they were marked to be located in the archives. The archives consisted of a set of compact discs which contained scanned copies of the medical records.

Inclusion Criteria

Subjects had to be Hospital or University HCP of UNC Chapel Hill who were prescribed HIV PEP for an occupational pathogen exposure from January 1, 2012 to May 12, 2016. This includes physicians, nurses, other healthcare personnel, and research staff. Potential HIV sources could be either known HIV positive, or of unknown HIV status. If there was any documentation of the source being found negative, then the employee was excluded from the data set. Employees were only included if they were prescribed the newer 3-drug regimen of raltegravir-emtricitabine-tenofovir. HCP given the older 4-drug regimen emtricitabine-tenofovir plus lopinavir-ritonavir were excluded from the analysis. Baseline demographics are provided in Table 2.

Exclusion of HCP taking the 4-drug regimen

Four HCP were not included in the analysis because they had received a 4-drug regimen (emtricitabine-tenofovir plus lopinavir-ritonavir) instead of the 3-drug regimen tenofovir-emtricitabine plus raltegravir.

Lab Values Collected

For each subject that passed the selection criteria, basic demographic information, pathogen exposure information (source HIV status and route of exposure), and laboratory values were obtained. The labs include white blood cell count (10^9/L), hemoglobin (g/dL), hematocrit (%), platelets (10^9/L), absolute neutrophil count (10^9/L), serum creatinine (mg/dL), total bilirubin (mg/dL), aspartate aminotransferase (U/L), alanine aminotransferase (U/L), and pregnancy test (either qualitative urine pregnancy or bHCG). These labs were recorded at baseline, 2 weeks, and 4 weeks, when available. Using Microsoft Excel 2013 (15.0.4823.1000) 32-bit, data was arranged, and descriptive statistics and calculations were carried out.

Definitions of Hematologic, Renal, and Hepatic Dysfunction

Definitions for hematologic, renal, and hepatic dysfunction were established based on the Common Terminology Criteria for Adverse Events (National Cancer Institute, 2010). The definitions are outlined in the following. For additional information, see the Appendix.

Definition of Hematologic Dysfunction

The hematologic dysfunction was defined by the presence of abnormalities in either hemoglobin or absolute neutrophil count. For our study, hematologic dysfunction was defined as any case where either hemoglobin <10.0 g/dL or ANC < 1.5x10^9/L.

Definition of Renal Dysfunction

Renal function was calculated by the glomerular filtration rate (GFR). Renal dysfunction is defined by a GFR less than 60 mL/min per 1.73 m^2. The GFR was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation, which is nearly as accurate as the 6-variable MDRD equation (Levey, et al., 2006). At McLendon Labs, the calibration of serum creatinine results had been set to enable traceability to the internationally accepted isotope dilution mass spectrometry. As such, for the calculation of the GFR, the constant 175 was used, as outlined by the equation:

$$GFR, \text{ in mL/min per } 1.73\ m^2 = 175 * Serumcreatinine^{-1.154} * Age^{-0.203} * (0.742 \text{ if female}) * (1.21 \text{ if black})$$

Definition of Hepatic Dysfunction

Hepatic dysfunction is defined as the presence of any of three conditions noted below. Of note, the upper limit of normal (ULN) at McLendon Labs for AST is 55 U/L, for ALT is 72 U/L, and for total bilirubin is 1.8 mg/dL.

- Condition 1: AST is greater than 3 times the upper limit of normal (ULN), that is, AST > 165 U/L
- Condition 2: ALT is greater than 3 times the upper limit of normal (ULN), that is, ALT > 216 U/L
- Condition 3: Total bilirubin is greater than 1.5 times the ULN, that is: total bilirubin > 1.8 mg/dL

Ethics Statement

This medical records review was performed after completing an IRB and receiving approval by expedited review from the Institutional Review Board at the University of North Carolina at Chapel Hill. The data was stored and secured onsite. All patient records were de-identified prior to analysis.

Results

Between January 1, 2012, and May 12, 2016, there were 78 HCP who were initially prescribed HIV PEP for an occupational exposure. Of those, 8 discontinued the PEP because the source patient was later confirmed to be HIV negative. Four HCP were prescribed the older regimen of emtricitabine-tenofovir plus lopinavir-ritonavir, and were also excluded from the original analysis. Two HCP had missing laboratory data, resulting in 64 HCP available for the final analysis.

The average age in the sample was 35 years (Table 1) with 57.9% female. The most frequently reported exposure was needlestick injury (61.3%). The vast majority of the exposures (93.5%) occurred in the clinical setting, as opposed to a research setting. The HIV status of the source was known 83.3% of the time. The majority of HCP starting PEP were hospital-based HCP (82.8%).

All HCP were HIV negative at baseline. There were no HIV seroconversions throughout the study. During the study period, no employee was prescribed a PEP regimen for more than one occasion. Two HCP presented with laboratory abnormalities at baseline based on the values

from the Common Terminology Criteria for Adverse Events (National Cancer Institute, 2010). Three HCP had abnormal changes at two weeks compared to baseline {renal (2), hematologic (1)}. As shown in Table 3, the number of hematologic, renal, and hepatic lab abnormalities was modest.

Hematologic Dysfunction

The lowest hemoglobin value in the data set was 10.8 g/dL. Thus, based on the hemoglobin values, there was no hematologic dysfunction. There was exactly one absolute neutrophil count (ANC) value below the threshold of $1.5 * 10^9$/L in the data sample. The patient had baseline ANC of $3.4 * 10^9$/L , and a 2-week value of $1.4 * 10^9$/L. There was no 4-week ANC recorded. The ANC of $1.4 * 10^9$/L falls into the Grade 2 category of ANC between $1.0 * 10^9$/L and $1.5 * 10^9$/L. The Grade 2 designation signifies a moderate adverse effect, or that minimal, local, or noninvasive intervention may be indicated.

Renal Dysfunction

On four occasions, the glomerular filtration rate (GFR) was below the 60 mL/min/1.73m^2 threshold (with one subject having 2 of these sub-threshold GFRs). One of the subjects had a GFR of 51.8 mL/min/1.73m^2 at baseline, and a GFR of 52.9 mL/min/1.73m^2 at week 2 (there was no week 4 serum creatinine measure taken). Another subject had baseline, 2-week, and 4-week GFRs of 73.3 mL/min/1.73m^2, 58.5 mL/min/1.73m^2, and 68.3 mL/min/1.73m^2 respectively. The third subject had baseline, 2-week, and 4-week GFRs of 69.5 mL/min/1.73m^2, 58.5 mL/min/1.73m^2, and 67.9 mL/min/1.73m^2 respectively. In both of the last 2 cases, the abnormal GFR occurred at week 2 and fully resolved by week 4 without intervention. Based on the Common Terminology Criteria for Adverse Events, all of the abnormal GFRs 51.8

mL/min/1.73m^2, 52.9 mL/min/1.73m^2, 58.5 mL/min/1.73m^2, and 58.5 mL/min/1.73m^2 fall into the Grade 2 category (GFR in the range of 30-59 mL/min/1.73m^2).

Hepatic Dysfunction

The highest aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the sample were 113 U/L and 183 U/L, respectively. As such, none of the AST or ALT values satisfied the criteria for hepatic dysfunction. One subject had a total bilirubin > 1.8 mg/dL on two separate occasions: on baseline (2.5 mg/dL) and at 4 weeks (1.9 mg/dL). The 2-week value was not recorded.

Four-Drug Regimen

Four subjects were excluded from the initial analysis because they were given the 4-drug regimen instead of the 3-drug regimen. The 4 subjects did not meet the criteria for hematologic (lowest hemoglobin: 10.8 g/dL, lowest ANC: 2.3 * 10^9/L), renal dysfunction (lowest GFR: 70.4 mL/min/1.73m^2), or hepatic dysfunction (highest AST: 81 U/L, highest ALT: 207 U/L, highest total bilirubin: 1.1 mg/dL).

Discussion

This study examined the HIV PEP protocol with a specific focus on the routine obtainment of laboratory values other than baseline HIV testing. For the 64 subjects in the time period, a total of 782 laboratory tests were drawn for hemoglobin, ANC, GFR, AST, ALT, and total bilirubin. Five laboratory abnormalities were identified in five different HCP: three were mild renal abnormalities, one was a mild hematologic abnormality, and one was a mild hepatic abnormality. In other words, 5/64 (8%) HCP exhibited laboratory abnormalities, and 5/782 (0.6%) laboratory tests were abnormal. None of the abnormalities necessitated PEP modification or discontinuation. It is important to note that the normal ranges for laboratory tests are

typically based on 95% confidence intervals. Thus if one conducts enough tests, one will inevitably detect cases with minor deviations from normal. Furthermore not every lab abnormality carries clinical significance.

These findings suggest that it is possible to eliminate routine laboratory testing before starting the currently recommended HIV PEP regimen in healthy HCP exposed to HIV. Although this study was carried out at a single academic institution, we believe that our findings are generalizable to other HCP at other institutions. Elimination of routine renal, hematologic and hepatic function studies in occupational HIV exposures should be considered as a way to improve the timeliness of starting PEP after exposure as well as eliminate the barrier of seeking immediate care after exposure beyond obtaining PEP medications.

Limitations

The retrospective nature of the study presented us with two main limitations. One was the measurement of adherence to the PEP regimen. While discontinuation of PEP therapy was documented in the occupational health record when the source patient testing was negative, there was often no explicit mention of adherence to the PEP regimen other than the filling of the prescription. However, several recent studies show that the adherence, in the nPEP setting, is quite high (Mayer, Mimiaga, Gelman, & Grasso, 2012).

Additionally, most of the HCP did not have laboratory studies at 4 weeks, since the PHS guidelines now recommend lab draws at baseline and 2 weeks (without explicitly mentioning of week 4). It is possible that laboratory values at 4 weeks may have shown some sub-clinical abnormalities but at that point the PEP regimen would be discontinued anyway.

Conclusion

Given our 5-year experience with the current tenofovir-emtricitabine-raltegravir regimen and systematic review of safety and efficacy data for this PEP regimen, we are recommending that occupational health providers no longer draw routine laboratory studies with the exception of baseline and subsequent HIV testing in healthy HCP. Focused laboratory testing may be indicated in HCP with underlying diseases (e.g., renal or hepatic dysfunction)

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Appendix

Table 1. Study Profiles of Systematic Review

Study Citation	Design	Population	Methods	Results	Quality Rating
(Rockstroh, et al., 2013)	STARTMRK was a randomized, blinded, double-dummy phase III trial of raltegravir with tenofovir/emtricitabine versus efavirenz with tenofovir/emtricitabine in treatment-naive HIV-infected adults.	586 people on 6 continents randomized 1:1 to RAL: EFV arms 281 people randomized to RAL group	Patient diaries and pill counts for adherence. Investigators monitored adverse events	Drug-related clinical adverse events in 146 raltegravir recipients (52.0%) Abnormal labs in 56 patients (19.9%) who received raltegravir Zero patients discontinued due to lab abnormalities	Good
(Eron, et al., 2011) (Eron, et al., 2011)	Randomized, controlled, double-blind phase 3 trial. Compared RAL daily to RAL BID	775 people on 6 continents randomized 1:1 to RAL BID: once-daily arms 382 randomized to RAL group	Patients completed diary cards for all study drugs Investigators monitored adverse events	Adverse events leading to discontinuation occurred in four (1%) 2.3% had *drug-related* lab abnormalities. 0 reports of serious drug related adverse effects, and discontinuations due to adverse effects	Good
(McAllister, et al., 2013)	Nonrandomized, controlled, prospective study. Comparing FTC-TDF with FTC-TDF-RAL	86 men prescribed FTC-TDF-RAL and 34 prescribed FTC-TDF) at 2 Australian clinics	Pill counts for adherence Investigators monitored adverse events	Adherence rate was 92%. Nine percent developed mild myalgias, with 4 developing transient grade 4 elevations in creatine kinase, which spontaneously resolved by week 4.	Fair

Table 2. Subject Demographics at Baseline (n=64)

Variable	
Mean age (years)	35.3 (± 10.3)
Age range (years)	21- 55]
Female	37 (57.9%)
Exposure route (n)	
- Needlestick	38 (61.3%)
- Splash	14 (22.6%)
- Laceration	17 (11.3%)
- Other	- 3 (4.8%)
- Missing	- 2
Exposure type (n)	
- Clinical	58 (93.5%)
- Non-clinical [a]	- 4 (6.5%)
- Missing	- 2
HIV status of source (n)	
- Known [b]	45 (83.3%)
- Unknown	- 9 (16.7%)
- Missing	- 10
Chart location (n)	
- Hospital OHS	53 (82.8%)
- UEOHC	11 (17.2%)

Abbreviations: HIV = human immunodeficiency virus; OHS = Occupational Health Services; UEOHC = University Employee Occupational Health Service

[a] Non-clinical exposure type category includes 3 exposures from HIV infected laboratory mice, and 1 exposure of a detention officer with an unknown source.

[b] The 'Known' category of HIV status of source includes 3 HIV infected laboratory mice.

Note: All percentages are calculated excluding the 'missing' values of the given characteristic.

Table 3: Number of Exposed HCP with Abnormal Lab Values per Time Period

	Baseline	**2weeks**	**4 weeks**
Hematologic dysfunction: hemoglobin, ANC (n)	0 / 60 Subject (53yo male): ANC 3.4 x 1.5x10^9/L	1 / 53 Subject (53yo male): ANC **1.4** [c] x 1.5x10^9/L	0 / 18 Subject (53yo male): ANC not recorded
Renal dysfunction: GFR (n)	1 / 61 [b] Subject (51yo female): GFR **51.8** [c] mL/min/1.73m^2 Subject (23yo female): GFR 69.5 mL/min/1.73m^2 Subject (64yo female): GFR 73.3 mL/min/1.73m^2	3 / 53 [b] Subject (51yo female): GFR **52.9** [c] mL/min/1.73m^2 Subject (23yo female): GFR **58.5** [c] mL/min/1.73m^2 Subject (64yo female): GFR **58.5** [c]	0 / 17 Subject (51yo female): No GFR recorded Subject (23yo female): GFR 67.9 mL/min/1.73m^2 Subject (64yo female): GFR 68.3 mL/min/1.73m^2
Hepatic dysfunction: AST, ALT, total bilirubin (n)	1 / 62 Subject (39yo male): Total bilirubin **2.5** [c] mg/dL	0 / 51 Subject (39yo male): total bilirubin not recorded	1 / 18 Subject (39yo male): Total bilirubin **1.9** [c] mg/dL

The denominators represent the number of HCP for which a given lab was drawn. Because the latest PHS guidelines recommend drug toxicity monitoring at baseline and 2 weeks (and not explicitly at week 4), fewer lab draws were done on week 4.

[a] n is the number of HCP who had no missing relevant laboratory data during the specified time frame

[b] The same employee appears in multiple time periods, that is, HCP were not removed from the sample if they had a hematologic, renal, or hepatic dysfunction.

[c] Denotes abnormal lab value, based on the Common Terminology Criteria for Adverse Events

Where absolute neutrophil count is ANC, and glomerular filtration rate is GFR

Data Dictionary

Variable	Description	Variable Type
DOB	Date of Birth: self-reported date of birth collected from the medical record.	Continuous
DOE	Date of exposure: self-reported date of exposure on the incident report.	Continuous
Age_on_Exp	Age on exposure: calculated by: Date of Exposure, minus the Date of Birth. Divided by 365. Rounded to the nearest integer. INT((DOE - DOE)/365)	Continuous
Sex	Sex: self-reported sex from the medical record. Female = 0, Male = 1.	Dichotomous
HIV_status_subj	HIV status of the subject: derived from the medical record. The result of an HIV test of the exposed employee after the exposure. HIV negative = 0, HIV Positive = 1	Dichotomous
WBC, HGB, HCT, PLATELETS, ANC, CREATININE, TBILI, AST, ALT, BHCG	Baseline labs for the WBC, Hgb, Hct, Platelets, ANC, Creatinine, Total Bilirubin, AST, ALT, Pregnancy test were obtained from EPIC, WebCIS, physical charts, or McLendon labs directly. To denote baseline, 2 week follow-up, and 4-week follow-up, each variable '_BASE' , '_FU2WEEK', and '_FU4WEEK' appended. For instance WBC_BASE, WBC_FU2WEEK, and WBC_FU4WEEK represent the WBC at baseline, 2 weeks, and 4 weeks respectively.	Continuous
Regimen	Regimen: the HIV PEP regimen was obtained from the provider notes in the medical record. Regimen: (Tenofovir+emtricitabine+raltegravir)=1, (emtricitabine+tenofovir+lopinavir+ritonavir) = 0	Dichotomous
EXP_TYPE	Exposure type: was determined by the type of work the employee was doing at the time of exposure. Research = 0, Clinical = 1.	Dichotomous
EXP_ROUTE	Exposure route: Determined by 1 of 4 categories in the incident report. Categories were splash, needlestick, laceration, and 'other'. 'other' included scratch, and cough.	Categorical
Dept	Department: derived from the incident report. If not available in the incident report, they were found in the university or hospital employee databases where available.	Categorical

Job_Title	Job Title: obtained from the incident report. If not available in the incident report, they were found in the university or hospital employee databases where available. The categories were based on the job titles.	Categorical
Source_HIV_Status	Source HIV Status: obtained from the incident report. If not present there, Source HIV Status was located in other sections of the medical record (provider's notes, confidential section, etc.)	Dichotomous
Chart_ Location	Chart Location: defines which occupational health clinic the exposed employee received follow-up (0=University Employee Occupational Health Services; 1= Hospital Employee OHS).	Dichotomous
Hgb2wk-baselineValue	Represents the percent change in Hgb from baseline. 100*(HGB_FU2WEEK - HGB_BASE)/ HGB_BASE	Continuous
Hgb4wk-baselineValue	Represents the percent change in Hgb from baseline. 100*(HGB_FU4WEEK - HGB_BASE)/ HGB_BASE	Continuous
ANC2wk-baselineValue	Represents the percent change in ANC from baseline. 100*(ANC_FU2WEEK - ANC_BASE)/ ANC_BASE	Continuous
ANC4wk-baselineValue	Represents the percent change in ANC from baseline. 100*(ANC_FU4WEEK - ANC_BASE)/ ANC_BASE	Continuous
GFR-GenderFactor	Based on Sex, variable. This is used in calculating the GFR. If Sex is Male (Sex=1), then GFR-GenderFactor = 1 If Sex is Female (Sex=0), then GFR-GenderFactor = 0.742	Dichotomous
GFR_Wk4(race=nonblk)	Glomeral filtration rate (GFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. $GFR = 175 * Serumcreatinine^{-1.154} * Age^{-0.203} * Sex * Race$ Where: Serumcreatinine is the Creatinine at that week; Age is the age on exposure; Sex is GFR-GenderFactor; Race is set to 1. The Race of the subjects could not be reliably retrieved with efficiency. As such, every subject was assumed to be nonblack. Since people who are nonblack have a lower GFR, this lead us to underestimate the GFR in black patients. (Per the MDRD equation, Black Race = 1.21, and nonblack Race = 1)	Continuous

Common Terminology Criteria for Adverse Events from the National Cancer Institute

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

(National Cancer Institute, 2010)

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen.					
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.					
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-

Renal and urinary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
Bladder perforation	-	Extraperitoneal perforation, indwelling catheter indicated	Intraperitoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.					

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.					
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-